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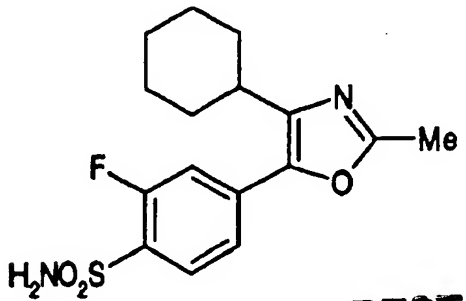
(54) Title: A POLYMORPH OF 5-(4-AMINOSULFONYL-3-FLUOROPHENYL)-4-CYCLOHEXYL-2-METHYLOXAZOLE

(57) Abstract: The object of the present invention is to provide novel polymorphs of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole having superior thermostability and excellent storage stability. A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole of Formula (I) wherein Me represents methyl group.




(I)



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# DESCRIPTION

## A Polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole

### Technical Field

The present invention relates to novel polymorphs of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (general name: tiracoxib), an excellent selective inhibitor of cyclooxygenase-2, the method for the production of them and the pharmaceutical compositions comprising them as the effective ingredient.

### Background Art

Generally, concerning pharmaceutical compounds and their compositions, it is known that the chemical and physical stability has a great influence on the effectiveness and safety. Especially, it is thought that the polymorphism is the important factor. The chemical and physical stability of a drug is also critical in the commercial development of the drug, because a drug, after being formulated, has to be transported and stored before it is taken. The environmental conditions which the drug experiences during the transportation and storage vary widely. So, a specific crystal form of a drug has to be found in order to make it sure that the drug is stable under such conditions of heat and humidity, and keeps its effectiveness and a high safety as a drug, by maintaining the quality required for it.

5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole and the production method of it have been disclosed

in the Example 2 of Japanese Patent No. 2636819. The present inventors have filed a patent application (Japanese Patent Application No. 1998-249621) relating to a novel production method of the compound, which differs from the one disclosed in the said patent.

Although Japanese Patent No. 2636819 discloses a specific crystal form of the present compound, 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole, there is no disclosure concerning the presence of different crystal forms of the compound, relationship between those different polymorphs, or the method how to maintain the quality of the product, which are crucial for industrial production of the compound.

Many literatures report that cyclooxygenase-2 takes part in various diseases and the inhibitors of the enzyme are effective to treat those diseases.

For example, it is reported in Cancer Res. (2000), 60(5), 1306-1311 that celecoxib, an inhibitor of cyclooxygenase-2, suppresses the growth of tumors (lung cancers, colon cancers, and so on).

It is reported in Clinical Therapeutics (1999), 21(9), 1497-1513 that celecoxib, an inhibitor of cyclooxygenase-2, is effective against rheumatoid arthritis and arthritis deformans.

It is reported in New England Journal of Medicine (2000), 342(26), 1946-1952 that celecoxib, an inhibitor of cyclooxygenase-2, is effective against familial adenomatous polyposis.

That the cyclooxygenase 2 inhibitors are useful against Alzheimer's disease is described in Presse Medicale (2000), 29(5), 267-273.

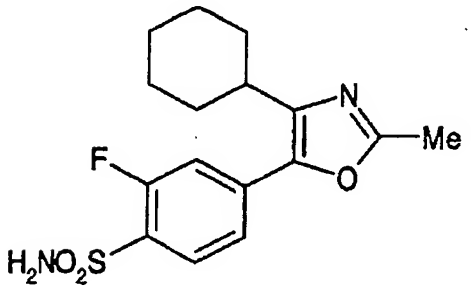
Disclosure of Invention

The present inventors have carried out extensive studies to solve the problems said above. As the result, they have found novel polymorphs of the compound stated below, and further studies based on this finding led them to the present invention.

Thus, the present invention relates to novel polymorphs of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as defined in the following items (1) to (20), the production method of the polymorphs and the pharmaceutical compositions comprising the novel polymorphs as active ingredient.

The present invention relates to:

(1) A substantially pure polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole having the structure of formula (I);




wherein Me represents methyl group.

(2) A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in (1) having a melting point of 168-169℃.

(3) A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in (1) characterized by an infrared absorption spectrum in potassium bromide with following peaks ($cm^{-1}$):

3494, 3340, 3244, 2930, 2852, 2354, 1610, 1556, 1481, 1446, 1423, 1410, 1382, 1340, 1309, 1273, 1256, 1225, 1165, 1147, 1087, 1078, 1033, 996, 970, 898, 871, 857, 824, 815, 771, 707, 676, 615, 584, 549, 520, 438, 420, 407.

(4) A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in (1) characterized by X-ray powder diffraction pattern (X-ray: Cu K-alpha 1/50kV/300mA; scintillation counter) with following diffraction angle and relative intensity:

TABLE 1

| Diffraction angle (2θ;°) | Relative intensity | Diffraction angle (2θ;°) | Relative intensity |
|---|---|---|---|
| 4.920 | 100 | 24.580 | 6 |
| 8.320 | 49 | 24.940 | 5 |
| 9.840 | 5 | 25.660 | 7 |
| 11.920 | 5 | 26.360 | 3 |
| 13.120 | 1 | 27.320 | 2 |
| 13.440 | 5 | 28.060 | 3 |
| 13.680 | 3 | 28.540 | 2 |
| 14.060 | 6 | 28.820 | 2 |
| 14.780 | 58 | 29.340 | 1 |
| 15.360 | 3 | 29.880 | 2 |
| 15.660 | 2 | 30.220 | 1 |
| 16.240 | 1 | 30.580 | 3 |
| 17.100 | 2 | 32.820 | 3 |
| 18.260 | 18 | 33.040 | 2 |
| 18.540 | 10 | 34.640 | 1 |
| 18.900 | 5 | 37.580 | 3 |
| 19.180 | 2 | 39.540 | 3 |
| 19.560 | 4 | 40.500 | 2 |
| 19.700 | 4 | 40.700 | 1 |
| 20.040 | 2 | 42.040 | 2 |
| 20.300 | 2 | 42.480 | 2 |
| 20.860 | 9 | 43.120 | 1 |
| 21.940 | 4 | 43.580 | 1 |
| 22.180 | 4 | 44.520 | 1 |
| 22.540 | 2 | 44.640 | 1 |
| 23.240 | 14 | 44.760 | 1 |
| 23.960 | 2 | 45.320 | 1 |
| 24.240 | 2 | 45.900 | 1 |

(5) A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in (1) having a transforming point of 149℃.

(6) A polymorph of 5-(4-aminosulfonyl-3-

fluorophenyl)-4-cyclohexyl-2-methyloxazole described in (1) characterized by an infrared absorption spectrum in potassium bromide with following peaks ($cm^{-1}$):

3314, 3104, 2932, 2858, 2654, 2352, 1609, 1573, 1557,1480,1452, 1407, 1385, 1339, 1309, 1292, 1277, 1260, 1225, 1171, 1150, 1086, 1077, 1029, 996, 970, 911, 898, 870, 828, 816, 773, 701, 679, 630, 615, 586, 550, 526, 457, 435, 411.

(7) A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in (1) characterized by a X-ray powder diffraction pattern (X-ray: Cu K-alpha 1/50kV/300mA; scintillation counter) with following diffraction angle and relative intensity:

TABLE 2

| Diffraction angle (2θ;°) | Relative intensity | Diffraction angle (2θ;°) | Relative intensity |
|---|---|---|---|
| 8.580 | 21 | 27.240 | 6 |
| 9.640 | 3 | 28.960 | 3 |
| 10.200 | 100 | 29.580 | 3 |
| 11.960 | 4 | 29.720 | 5 |
| 12.180 | 3 | 30.200 | 4 |
| 15.320 | 14 | 30.440 | 7 |
| 15.980 | 10 | 30.780 | 3 |
| 17.060 | 44 | 31.200 | 10 |
| 17.220 | 15 | 32.240 | 3 |
| 18.080 | 35 | 32.640 | 7 |
| 19.500 | 15 | 34.820 | 7 |
| 21.020 | 14 | 35.140 | 3 |
| 21.920 | 3 | 36.520 | 5 |
| 22.080 | 3 | 38.840 | 5 |
| 22.400 | 10 | 39.900 | 5 |
| 22.700 | 7 | 40.740 | 6 |
| 22.960 | 7 | 41.000 | 12 |
| 23.700 | 5 | 43.740 | 5 |
| 23.880 | 9 | 43.900 | 7 |
| 24.340 | 13 | 46.740 | 3 |
| 24.660 | 10 | 46.820 | 3 |
| 25.480 | 5 | 50.060 | 4 |
| 25.940 | 82 | | |

(8) A method for preparing the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in any of (2) to (4), which comprises the step of crystallizing 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole in a mixture of methanol and water at a temperature of 60℃ or higher.

(9) A method for preparing the polymorph of 5-(4-

aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in any of (2) to (4), which comprises the step of crystallizing 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole in a mixture of isopropyl alcohol and water at a temperature of 60℃ or higher.

(10) A method for preparing the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in any of (5) to (7), which comprises the step of crystallizing 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole from a mixture of acetone and water.

(11) A method for preparing the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in any of (5) to (7), which comprises the step of crystallizing 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole from ethanol.

(12) A pharmaceutical composition comprising as an active ingredient the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in (1).

(13) A pharmaceutical composition comprising as an active ingredient the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in any of (2) to (4).

(14) A pharmaceutical composition comprising as an active ingredient the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in any of (5) to (7).

(15) A prophylactic and/or therapeutic agent for the treatment of a disease caused by cyclooxygenase-2 comprising as an active ingredient the polymorph of 5-(4-

aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in (1).

(16) A prophylactic and/or therapeutic agent for the treatment of a disease caused by cyclooxygenase-2 comprising as an active ingredient the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in any of (2) to (4).

(17) A prophylactic and/or therapeutic agent for the treatment of a disease caused by cyclooxygenase-2 comprising as an active ingredient the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole described in any of (5) to (7).

(18) A prophylactic and/or therapeutic agent described in any of (15) to (17), wherein the disease caused by cyclooxygenase-2 is at least one member selected from the group consisting of arthritis, gout or ankylosing spondylitis, asthma, bronchitis, menstrual cramp, dysmenorrhea, premature labour, myositis, bursitis, synovitis, skin related disease, post-operative inflammation, gastrointestinal disease, cancer or metastases of the cancer, cellular neoplastic transformations or metastatic tumor growth, tumor angiogenesis, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, type II diabetes, nephrotic syndrome, Behcet's disease, polymyositis, gingivitis, nephritis, hypersensitivity, ophthalmic disease, disease mediated by influenza or other viral infections, common cold, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, post-operative pain, dental pain, muscular pain, neuralgia,

lumbago, neck pain, headache, sprains and strains, pain resulting from cancer, glaucoma, osteoporosis, autoimmune disease or diabetic retinopathy.

(19) A prophylactic and/or therapeutic agent described in (18), wherein the disease caused by cyclooxygenase-2 is arthritis.

(20) A prophylactic and/or therapeutic agent described in (19), wherein arthritis is rheumatoid arthritis.

(21) A prophylactic and/or therapeutic agent described in (19), wherein arthritis is osteoarthritis.

(22) A prophylactic and/or therapeutic agent described in (18), wherein the disease caused by cyclooxygenase-2 is familial adenomatous polyposis.

(23) A prophylactic and/or therapeutic agent described in (18), wherein the disease caused by cyclooxygenase-2 is cancer or metastases of the cancer.

(24) A prophylactic and/or therapeutic agent described in (18), wherein the disease caused by cyclooxygenase-2 is central nervous system disorder.

(25) A prophylactic and/or therapeutic agent described in (24), wherein the central nervous system disorder is Alzheimer's disease.

(26) A prophylactic and/or therapeutic agent described in (18), wherein the disease caused by cyclooxygenase-2 is osteoporosis.

(27) 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole which has the melting point described in (2), and the infrared absorption maxima in potassium bromide described in (3), and the X-ray powder diffraction pattern described in (4), and the transforming point of 149℃.

(28) 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-

methyloxazole, which has the infrared absorption maxima in potassium bromide described in (6), and the X-ray powder diffraction pattern described in (7), and the transforming point of 149℃.

The term "polymorph" used here means one of the different crystalline forms of the same compound. For example, in case of carbon, diamond, carbon black and graphite are polymorphs.

One object of the present invention, therefore, is to provide very stable polymorphs of tiracoxib, and the other one is to provide the production method of the polymorphs. A further object of the present invention is to provide pharmaceutical composition which is consist of pharmacologically effective amount of the polymorph said above and other ingredients such as fillers which are pharmacologically allowable.

The novel polymorphs of the compound of the present invention are useful not only as antipyretics, analgesics, and the anti-inflammatory agents, but they are useful as the agents for treating such diseases and syndromes as arthritis including rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, and juvenile arthritis; gout or ankylosing spondylitis; asthma; bronchitis; menstrual cramps; dysmenorrhea; premature labor; tenositis; myositis; bursitis; synovitis; hepatopathy including hepatitis; skin-related diseases including such as psoriasis, eczema, burns and dermatitis; post-operative inflammation after ophthalmic surgery such as cataract surgery and refractive surgery; gastrointestinal diseases such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis; familial adenomatous polyposis; cancers

such as colorectal cancer, breast cancer, lung cancer, prostatic cancer, bladder cancer, cervical cancer, cancer of the uterine cervix and skin cancer, as well as metastases of those cancers; cellular neoplastic transformations or metastatic tumor growth; tumor angiogenesis; inflammatory diseases including such angiopathies as atherosclerosis; migraine headaches; periarteritis nodosa; thyroiditis; aplastic anemia; Hodgkin's disease; scleroderma; rheumatic fever; type I diabetes; type II diabetes; neuromuscular junction diseases including myasthenia gravis; white matter diseases including multiple sclerosis; sarcoidosis; nephrotic syndrome; Behcet's disease; polymyositis; gingivitis; nephritis; hypersensitivity; swelling occurring after injury; myocardial ischemia; ophthalmic diseases such as retinitis, retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue; symptoms associated with influenza or other viral infections; common cold; central nervous system diseases such as cortical dementia including Alzheimer's disease; central nervous system damage caused by stroke, ischemia and trauma; allergic rhinitis; respiratory distress syndrome; endotoxin shock syndrome; post-operative pain; dental pain; muscular pain; neuralgia; lumbago, neck pain; headache; sprains; strains; pain resulting from cancer; glaucoma; osteoporosis; autoimmune disease or diabetic retinopathy.

More preferably, the compounds of the present invention are used for the treatment of arthritis including rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, and juvenile arthritis; gout and ankylosing spondylitis; asthma; bronchitis;

menstrual cramps; dysmenorrhea; premature labor; myositis; bursitis; synovitis; skin-related diseases including such as psoriasis, eczema, burns and dermatitis; post-operative inflammation after ophthalmic surgery such as cataract surgery and refractive surgery; gastrointestinal diseases such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis; familial adenomatous polyposis; cancers such as colorectal cancer, breast cancer, lung cancer, prostatic cancer, bladder cancer, cervical cancer, cancer of the uterine cervix and skin cancer, as well as metastases of those cancers; cellular neoplastic transformations and metastatic tumor growth; tumor angiogenesis; migraine headaches; periarteritis nodosa; thyroiditis; aplastic anemia; Hodgkin's disease; scleroderma; rheumatic fever; type I diabetes; type II diabetes; nephrotic syndrome; Behcet's disease; polymyositis; gingivitis; nephritis; hypersensitivity; myocardial ischemia; ophthalmic diseases such as retinitis, retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue; symptoms associated with influenza or other viral infections; common cold; central nervous system diseases such as cortical dementia, including Alzheimer's disease; allergic rhinitis; respiratory distress syndrome; endotoxin shock syndrome; post-operative pain; dental pain; muscular pain; neuralgia; lumbago, neck pain; headache; sprains; strains; pain resulting from cancer; glaucoma; osteoporosis; autoimmune disease and diabetic retinopathy. And, most preferably, they are used for the treatment of arthritis including rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, and

juvenile arthritis; gout; asthma; bronchitis; dysmenorrhea; skin-related diseases including such as psoriasis, eczema, burns and dermatitis; gastrointestinal diseases such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis; familial adenomatous polyposis; cancers such as colorectal cancer, breast cancer, lung cancer, prostatic cancer, bladder cancer, cervical cancer, cancer of the uterine cervix and skin cancer, as well as metastases of those cancers; cellular neoplastic transformations and metastatic tumor growth; tumor angiogenesis; migraine headaches; aplastic anemia; gingivitis; ophthalmic diseases such as retinitis, retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue; symptoms associated with influenza or other viral infections; common cold; central nervous system diseases such as cortical dementia including Alzheimer's disease; allergic rhinitis; post-operative pain; dental pain; muscular pain; neuralgia; lumbago, neck pain; headache; sprains; strains; pain resulting from cancer; glaucoma and osteoporosis.

In cases where the polymorphs of the present invention are made into pharmaceutical formulations, they may usually be mixed, according to the method known in itself, with pharmacologically allowable carriers, fillers, diluents, disintegrants, stabilizers, preservatives, buffering agents, emulsifying agents, aromatics, colorings, sweeteners, viscid agents, flavoring agents, and other additives, concrete examples thereof being water, vegetable oils, alcohols such as ethanol and benzyl alcohol, polyethylene glycol, glycerol triacetate, gelatine, carbohydrates such as lactose and starch, magnesium stearate, talc, lanolin, vaseline and so on, and then formed

into tablets, pills, powders, granules, suppositories, injecting drugs, eye-lotions, liquids, capsules, troches, aerosols, elixirs, suspensions, emulsions and syrups and so on, appropriate for administration per os or parenterally.

The administration dose may vary depending on the kind of disease and the severity of the disease, compounds to be administered, route of administration, age, sex and body weight of each patient. In case of oral administration, the dose may be selected, in general, preferably from the range of about 0.1 to 1000mg, and more preferably from the range of about 1mg to 300mg, and the most preferably from the range of about 5mg to 200mg for an adult per day.

Furthermore, the compounds of the present invention can be used as medicines not only for human use, but for veterinary use.

The polymorph of the present invention can be produced by the methods of crystallization described below. However, it will be apparent that the production method is not restricted to the ones described here.

The compound 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole itself may be produced according to the method described in the specification of Japanese Patent No. 2636819 and/or of Japanese Patent Application No.1998-249621.

In the description which follows, the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole having the melting point of 168 to 169℃, infrared absorption wave numbers in potassium bromide described above, a X-ray powder diffraction pattern given in Table 1, and the transformation

temperature of 149℃ is defined Form A, and the another polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole which has infrared absorption wave numbers in potassium bromide described above, a X-ray powder diffraction pattern given in Table 2, and the transformation temperature to Form A of 149℃ is defined Form B.

(1)Polymorph Form A

This polymorph can be produced by crystallizing 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole either from mixed solvents of methanol-water, ethanol-water and isopropyl alcohol-water or from solvents such as toluene, xylene and water, which have only limited solubility for the objective compound, at the temperature of about 50℃ or higher, and more preferably at about 60℃ or higher, but below the boiling point of the solvent or solvent mixtures used. The crystallization process may include the operation of crystal growth.

(2)Polymorph Form B

This polymorph can be produced by crystallizing 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole either from organic solvents such as acetone, ethanol, ethyl acetate, methyl ethyl ketone, water or the mixtures thereof, at the temperature of about 50℃ or lower, and more preferably at about 40℃ or lower, and above the melting point of the solvent or solvent mixtures used.

Brief Description of Drawings

FIG. 1 shows the results of the differential scanning calorimetry (DSC) measurement of the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole

(Form A).

FIG. 2 shows the results of the differential scanning calorimetry (DSC) measurement of the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (Form B).

FIG. 3 shows the infrared absorption spectrum of the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (Form A) in potassium bromide.

FIG. 4 shows the infrared absorption spectrum of the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (Form B) in potassium bromide.

FIG. 5 shows the X-ray powder diffraction pattern of the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (Form A).

FIG. 6 shows the X-ray powder diffraction pattern of the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (Form B).

Best Mode for Carrying Out the Invention

The following examples and experimental examples are given for the purpose of illustrating the present invention in more detail. The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiment is therefore to be considered in all respects as illustrative and not restrictive.

Example 1

Production of the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (Form A)

Partially purified 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (850.0 g) was suspended in methanol (2125 ml) and the suspension was heated up to 65℃ to dissolve the material. Active charcoal (42.5 g) was then added and the mixture was stirred at 65℃ for one hour. The active charcoal was then removed by filtration under pressure, and the dissolving flask and the filtering apparatus used were rinsed with methanol (425 ml), and the washings was combined with the main filtrate. The combined filtrate and washings was then poured into pure water (5100 ml) prepared in a separate vessel, and the resulting mixture was heated up to 80℃ and stirred at the same temperature for two hours, followed by cooling to 20℃ (inner temperature) and stirring at the same temperature for one hour. Then, the resulting mixture was filtered, and crystals obtained were washed with pure water (1700 ml) and dried *in vacuo* giving the titled compound as white crystals (810.0 g, in a yield of 95%).

Example 2

Preparation of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (Form A)

Partially purified 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (50.0 g) was suspended in isopropyl alcohol (150 ml) and the suspension was heated up to 80℃ to dissolve the material. Active charcoal (1.5 g) was then added and the mixture was stirred at 80℃ (inner temperature) for one hour. After the stirring, the active charcoal was then removed by filtration under pressure, and the dissolving flask and the filtering apparatus used were rinsed with isopropyl

alcohol (25 ml), and the washings was combined with the main filtrate. The combined filtrate and washings were then poured into pure water (525 ml) prepared in a separate vessel, and the resulting mixture was heated up to 75℃ (inner temperature) or higher and stirred at the same temperature for two hours, followed by cooling to 20℃ (inner temperature) and stirring at the same temperature for one hour. Then, the resulting mixture was filtered, and crystals obtained were washed with pure water (40 ml) and dried *in vacuo* giving the titled compound as white crystals (48.1 g, yield: 96%).

Example 3

Preparation of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (Form B)

A suspension of partially purified 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (10.0 g) in a mixed solvent of acetone (50 ml) and water (50 ml) was heated under reflux to get a clear solution, followed by gradual cooling to 45℃ (inner temperature) to induce crystallization, and the mixture was kept at the same temperature for two hours to assure complete separation of crystals. The resulting solution containing crystals was cooled to room temperature and filtered. The crystals obtained were then washed with a mixture of acetone and water (1:1)(30 ml) and then dried *in vacuo* giving the titled compound as white crystals (7.7 g, yield: 77%).

Example 4

Preparation of the polymorph (Form B) of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole

A suspension of partially purified 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (10.0 g) in ethanol (40 ml) was heated under reflux to get a clear solution, followed by gradual cooling to 40℃ (inner temperature) to induce crystallization, and the mixture was kept at the same temperature for two hours to assure complete separation of crystals. The resulting solution containing crystals was cooled to room temperature and filtered. The crystals obtained were then washed with ethanol (30 ml) and then dried *in vacuo* giving the titled compound as white crystals (6.8 g, yield: 68%).

Experimental Example 1: Differential Scanning Calorimetry (DSC) Measurements of the Polymorphs of the Present Invention

Each 10 mg of the polymorphs of the present invention and aluminum oxide was taken in separate pans made of aluminum and set in a thermal analyzer (Rigaku Co. Ltd.: TG8110c), after the weight of those materials having been measured precisely. The DSC measurements were made under operational conditions described below, referring the aluminum oxide as the standard. Figure 1 and 2 show the results of the measurements with Form A and Form B, respectively.

Operational conditions

Reagent : aluminum oxide

Rate of the temperature raising: 5℃/minute

Temperature range: 60-250℃

Atmosphere: open

Experimental Example 2: Infrared Absorption Spectrum Measurements of the Polymorphs of the Present Invention

Using each 5 mg of the polymorphs of the present invention, infrared spectrum measurements were carried out according to the Potassium Bromide Tablet Method in the General Test Methods of the Japanese Pharmacopoeia. The ratio of the polymorph sample to potassium bromide used was 1/100. The results of the measurements with Form A and Form B are shown in Figure 3 and Figure 4, respectively.

Experimental Example 3: X-ray Powder Diffraction Measurements of the polymorphs of the present invention

Each 150 mg of the polymorphs of the present invention was charged in the sample mounting position of a glass sample plate, and the measurement was carried out using an X-ray powder diffractometer (Rigaku Co. Ltd., RINT 2500H), under operational conditions which follow. The results obtained with Form A and Form B are shown in Figure 5 and Figure 6.

X-ray: Cu $\alpha$, 50 KV, 300 mA
Scan mode: continuous
Rate of scanning: 4° /minute
Step of scanning: 0.02°
Scanning axis: $2\theta/\theta$
Scanning range: 3-60°
Divergence slit: 1/2°
Scattering slit: 1/2°
Receiver slit: 0.15 mm

The results of the testing regarding to the stability of the polymorph of the present invention were as follows.

Experimental Example 4: Appearance Test

Samples of the polymorphs of the present invention were stored in an atmosphere of temperature, 60℃, and humidity, 75%, for two weeks, and the appearances of the samples were compared with those of the untreated ones. The comparison was made by observing the samples in beakers placed on a white paper. The results are shown in Table 4.

Experimental Example 5: Moisture Determination

Samples of the polymorphs of the present invention were stored in an atmosphere of temperature, 60℃, and humidity, 75%, for two weeks, and the water contents of them before and after the storage were measured and compared. The water content was measured according to the Direct Titration Method in the Water Content Measuring Methods in the General Test Methods of the Japanese Pharmacopoeia, by using the Karl Fischer's Water Meter and Karl Fischer's reagent. Each 0.3 g portion of the polymorph was weighed accurately and the water content of it was measured. The results are shown in Table 4.

Experimental Exanoke 6: Purity Determination

(Preparation of the mobile phase A solution)

A solution of potassium dihydrogenphosphate prepared by dissolving 3.40 g of potassium dihydrogenphosphate in distilled water and adjusting the total volume to 2500 ml, and a solution of disodium hydrogenphosphate prepared by dissolving 0.71 g of disodium hydrogenphosphate in water and adjusting the total volume to 500 ml, were mixed and the pH of the resulting mixture was adjusted to 6.0. To 1800 ml of this mixture was added 1200

ml of acetonitrile to give the mobile phase A solution.

(Preparation of the mobile phase solution B)

A solution of potassium dihydrogenphosphate prepared by dissolving 3.40 g of potassium dihydrogenphosphate in distilled water and adjusting the total volume to 2500 ml, and a solution of disodium hydrogenphosphate prepared by dissolving 0.71 g of disodium hydrogenphosphate in water and adjusting the total volume to 500 ml, were mixed and the pH of the resulting mixture was adjusted to 6.0. To 600 ml of this mixture was added 2400 ml of acetonitrile to give the mobile phase B solution.

Samples of the polymorphs of the present invention were stored in an atmosphere of temperature, 60℃, and humidity, 75%, for two weeks. The purity of the samples was measured before and after the storage using a liquid chromatograph as follows.

Each 0.04 g of the polymorph was weighed accurately, dissolved in the mobile phase A solution, and the total volume of the solution was adjusted to accurately to 20 ml to give the sample solution. Precisely 1 ml of this solution was diluted with the mobile phase A solution to 100 ml accurately, to give the standard solution (1 %). Each 50 μl of the sample and the standard solutions was analyzed according to the Liquid Chromatography Method in the General Test Methods of the Japanese Pharmacopoeia, under the conditions described below. The peak area of each peak was determined by using an automated integration method and the content of each impurity (%) and the total content of the impurities (%) were calculated. The results are shown in Table 4.

[Value 1]

$$\text{Impurity (\%)} = \frac{\text{(Peak area of each peak except for the one due to the polymorph, determined with the sample solution)}}{\text{(Peak area of the polymorph determined with the standard solution)}} \times 100$$

[Value 2]

$$\text{The total impurity (\%)} = \frac{\text{(The sum of the peak areas of the peaks except for the one due to the polymorph, determined with the sample solution)}}{\text{(Peak area of the polymorph determined with the standard solution)}} \times 100$$

The operational conditions under which the above chromatographic measurements were made are as follows:

Detector: a ultra-violet spectrometer (wave lengths used for the measurement: 220 nm and 290 nm)

Column: a stainless steel tube of 4.6 mm in diameter and 15 cm in length, packed with a silica gel for chromatographic use of 5 $\mu$m in size on which octadecyl groups are bonded chemically.

Column temperature: the temperature was kept constant at a temperature of about 40℃.

Mobile phase: The mobile phase A and B solutions were used according to the time-program as shown in Table 3.

[Table 3]

TABLE 3: THE TIME PROGRAM

| Time (minutes) | Mobile phase A (%) | Mobile phase B (%) |
|---|---|---|
| 0 | 100 | 0 |
| 20 | 100 | 0 |
| 40 | 0 | 100 |
| 60 | 0 | 100 |
| 61 | 100 | 0 |
| 75 | 100 | 0 |

Flow rate: The flow rate was adjusted so that the polymorph is to be eluted at 13 minutes, when 50 $\mu$l of the standard solution was applied (1 ml/minute).

Detector sensitivity: The sensitivity was adjusted so that the peak height of the peak due to polymorph will be 30 to 50 % of the full scale, when 50 $\mu$l of the standard solution was applied.

Integration duration: 75 minutes

Experimental Example 7: Quantification Test

(Preparation of the mobile phase)

A solution of potassium dihydrogenphosphate prepared by dissolving 3.40 g of potassium dihydrogenphosphate in distilled water and adjusting the total volume to 2500 ml, and a solution of disodium hydrogenphosphate prepared by dissolving 0.71 g of disodium hydrogenphosphate in distilled water and adjusting the total volume to 500 ml, were mixed and the pH of the resulting mixture was adjusted to 6.0. To 1500 ml of this mixture was added 1500 ml of acetonitrile to give the mobile phase.

(Preparation of the internal standard solution)

An internal standard solution was prepared by diluting 1 ml of n-propyl benzoate 2000 times with the mobile phase.

Samples of the polymorphs of the present invention were stored in an atmosphere of the temperature, 60℃, and the humidity, 75%, for two weeks. The samples before and after the storage were quantitatively determined by means of liquid chromatography as follows.

Each 0.025 g of the polymorphs and the standard sample was weighed precisely, dissolved in the mobile phase, and adjusted to a volume of 50 ml, accurately. Then, each precisely 5 ml of these solutions was taken separately. To each of them was added each precisely 5 ml of the internal standard, adjusted the total volume to 50 ml, accurately, to get the sample and standard solutions. Each 20 $\mu$l of the sample and the standard solutions was analyzed according to the Liquid Chromatograph Method in the General Testing Methods of the Japanese Pharmacopoeia, under conditions described below. First, Qt, that is, the ratio of the peak area of the polymorph to that of the internal standard, and Qs, that is, the ratio of the peak area of the standard sample to that of the internal standard, were calculated. And then, a quantitative value of polymorph was determined with each sample, according to the equation below. It was necessary, prior to the calculation of Qt and Qs, to get the weight of each polymorph on a dry basis based on the water content of each sample and of the standard sample.

[Value 3]

$$\text{Quantitative value of polymorph (\%)} = \frac{\text{(The weight of the standard sample of the polymorph on a dry basis (mg))} \times Qt}{\text{(The weight of the sample of the polymorph on a dry basis (mg))} \times Qs} \times 100$$

The operational conditions under which the above liquid chromatographic measurements were made are as follows:

Detector: a ultra-violet spectrometer (wave lengths used for the measurement: 220 nm)

Column: a stainless steel tube of 4.6 mm in diameter and 15 cm in length, packed with a silica gel for chromatographic use of 5 μm in size on which octadecyl groups are boud chemically.

Column temperature: the temperature was kept constant at a temperature of about 40℃.

Flow rate: The flow rate was adjusted so that the polymorph is to be eluted at 6 minutes (1 ml/minute).

[Table 4]

TABLE 4: STABILITY TEST

| Polymorphic Crystals | Storage Conditions | Period | Appearances | Water Content (%) | Purity(%) | | Quantitative Value |
|---|---|---|---|---|---|---|---|
| | | | | | maximum | Total | |
| Form A | Initial state | | white | 0.61 | 0.24 | 0.41 | 100.2 |
| | 60℃/75% | 2 weeks | white | 0.74 | 0.24 | 0.38 | 100.2 |
| Form B | Initial state | | white | 0.06 | 0.06 | 0.08 | 101.0 |
| | 60℃/75% | 2 weeks | white | 0.07 | 0.06 | 0.08 | 101.1 |

Experimental Example 8: Solubility Test

(Preparation of the mobile phase)

Acetonitrile and distilled water were mixed in the ratio of 1:1 to give the mobile phase

(Preparation of the standard solution)

Standard solutions which contain 2, 4, 6, 8, and 10 μl of the polymorph of the present invention, respectively, were prepared by precisely weighing 25 mg of the polymorph of the present invention, dissolving it in the mobile phase, adjusting the volume to 50 ml, and diluting the resulting solution with the mobile phase.

By using these solutions, a standard calibration curve was made.

(Preparation of the sample solutions)

The polymorph of the present invention was ground in a mortar, and 10 mg of it was weighed precisely and transferred into a 50-ml centrifuge tube, followed by addition of 20 ml of distilled water. The mixture was then stirred at 25℃ for 3 hours. After stirring, the solution was filtered. The first

12 ml of the filtrate was discarded and the next 5ml of the filtrate was taken, transferred to a 10 ml flask and diluted with acetonitrile to a volume of 10 ml.

Each 20 μl of the sample and the standard solutions was analyzed according to the Liquid Chromatograph Method in the General Testing Method of the Japanese Pharmacopoeia under the conditions described below, and the peak area was determined with each sample. The concentration of the polymorph was calculated by means of the calibration curve made as described above. The results are shown in Table 5.

The operational conditions under which the above liquid chromatographic measurements were made are as follows:

Detector: a ultra-violet spectrometer (wave lengths used for the measurement: 220 nm)

Column: a stainless steel tube of 4.6 mm in diameter and 15 cm in length, packed with a silica gel for chromatographic use of 5 μm in size on which octadecyl groups are bonded chemically.

Column temperature: the temperature was kept constant at a temperature of about 40℃.

Flow rate: The flow rate was adjusted so that the polymorph is to be eluted at 6 minutes (1 ml/minute).

[Table 5]

TABLE 5: SOLUBILITY TEST

| Polymorphic Crystals | Solubility in Water (μg/ml) |
|---|---|
| Form A | 13 |
| Form B | 8 |

Experimental Example 9: Growth Suppression Action on Non-small-cell Lung Cancer (NSCLC)

Tumor cell growth suppression action of the compounds of the present invention can be confirmed with NSCLC cells as object by the ordinary MTT ([3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide]) assay method (J. Immunol. Mehods (1983), 65, 55-63).

The test results showed that the compounds of the present invention have an excellent cell growth suppression action.

Experimental Example 10: Lung Cancer Suppression Action

Subcutaneous transplantation-natural metastasis model (LNM35) mice are prepared by transplanting subcutaneously human lung cancer cell line in SCID mice. The mice are divided into two groups; one is treated with the compound of the present invention and the other not. After tens of days, the tumor size at the transplanted site and the presence or absence of lymphatic metastasis in the treated group are compared with those in the untreated one to assess the lung cancer suppression action of the compound.

The test results showed that the compounds of the present invention have an excellent lung cancer growth suppression action.

Experimental Example 11: Lung Cancer Development Suppression Action

NNK [4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone]-induced lung cancer developing model mice are prepared by using A/J mice. The mice are divided into two groups; one

is treated with the compound of the present invention and the other not. The presence or absence of development of lung cancer in the treated group is compared with that of the untreated one with respect to time after NNK has been given, to assess the lung cancer development suppression action of the compound.

The test results showed that the compounds of the present invention have an excellent lung cancer development suppression action.

Experimental Example 12: Esophagus Cancer Suppression Action

NMBA-induced esophagus cancer development model rats are prepared by using F344 rats. The rats are divided into two groups; one is treated with the compound of the present invention and the other not. After a given period of time from the start of administration of the compound, the number and volume of tumors in the treated group are compared with those in the untreated one to assess the esophagus cancer suppression action of the compound.

The test results showed that the compounds of the present invention have an excellent esophagus cancer suppression action.

Experimental Example 13: Large Intestine ACF (Aberrant Crypt Foci) Generation Suppression Action

DMH (dimethylhydrazine)-induced large intestine tumor generation model rats are prepared by using Fischer strain of rats. The rats are divided into two groups; one is treated with the compounds of the present invention and the other not. After a given period of time from the start of administration of the compound, the number of AFC formed in the treated group is compared

with that in the untreated one to assess the large intestine ACF generation suppression action.

The test results showed that the compounds of the present invention have an excellent large intestine ACF generation suppression action.

Experimental Example 14: Large Intestine Cancer Suppression Action

A large intestine tumor cell line is transplanted in the back of Balb/c mice. The mice are divided into two groups; one is treated with the compounds of the present invention and the other not. The size of the tumor at the transplanted site in the treated group is measured with respect of time and compared with that in the untreated one to assess the large intestine cancer suppression action of the compounds.

Experimental Example 15: Lung Metastasis Suppression Action

Lung metastasis model mice are prepared by injecting tumor cells via tail vein. The mice are divided into two groups; one is treated with the compound of the present invention and the other not. After a given period of time after the tumor cells have been injected, the number of lung metastasis in the treated group is compared with that in the untreated one to assess the lung metastasis suppression action of the compound.

The test results showed that the compounds of the present invention have an excellent lung metastasis suppression action.

Experimental Example 16: Liver Metastasis Suppression Action

Liver metastasis model mice are prepared by injecting tumor

cells into pancreas of mice. The mice are divided into two groups; one is treated with the compound of the present invention and the other not. After a given period of time after the tumor cells have been injected, the number of liver metastasis in the treated group is compared with that in the untreated one to assess the liver metastasis suppression action of the compound.

Experimental Example 17: Bone Metastasis Suppression Action

Cells of a mouse breast cancer cell line and mouse bone marrow cells are co-incubated in the presence and absence of the compound of the present invention. After a given period of time, the number of osteoclast cells in the treated culture is compared with that in the untreated one to assess the bone metastasis suppression action.

The test results showed that the compounds of the present invention have an excellent bone metastasis suppression action.

Experimental Example 18: Neurite Elongation Promotion Action

NG cells in which cyclooxygenase 2 is expressed by means of the cyclooxygenase expression vector are incubated in the presence and absence of the compound of the present invention. The length of the neurites of the treated and untreated cells is determined under a microscope with respect of time and compared to assess the neurite elongation promotion action of the compound.

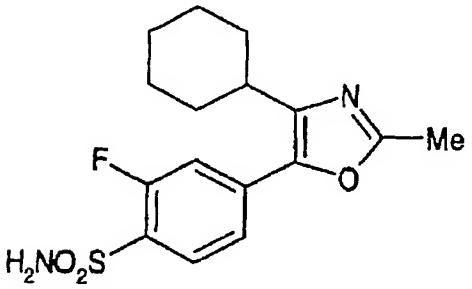
The results showed that the compounds of the present invention have an excellent neurite elongation promotion action.

Industrial Applicability

Among others, the test results described above clearly show that the polymorphs of the present invention have superior stability, and that they will keep their quality and pharmacological effectiveness under various environmental conditions encountered during distribution and storage. Furthermore, the compounds of the present invention have excellent therapeutic effects against various diseases in which cyclooxygenase 2 is involved.

CLAIMS

1. A substantially pure polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole having the structure of formula (I);




wherein Me represents methyl group.

2. A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in claim 1 having a melting point of 168-169℃.

3. A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in claim 1, which is characterized by an infrared absorption spectrum in potassium bromide with following peaks ($cm^{-1}$):

3494, 3340, 3244, 2930, 2852, 2354, 1610, 1556, 1481, 1446, 1423, 1410, 1382, 1340, 1309, 1273, 1256, 1225, 1165, 1147, 1087, 1078, 1033, 996, 970, 898, 871, 857, 824, 815, 771, 707, 676, 615, 584, 549, 520, 438, 420, 407.

4. A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in claim 1, which is characterized by X-ray powder diffraction pattern

(X-ray: Cu K-alpha 1/50kV/300mA; scintillation counter) with following diffraction angle and relative intensity;

| Diffraction angle (2θ;°) | Relative intensity | Diffraction angle (2θ;°) | Relative intensity |
|---|---|---|---|
| 4.920 | 100 | 24.580 | 6 |
| 8.320 | 49 | 24.940 | 5 |
| 9.840 | 5 | 25.660 | 7 |
| 11.920 | 5 | 26.360 | 3 |
| 13.120 | 1 | 27.320 | 2 |
| 13.440 | 5 | 28.060 | 3 |
| 13.680 | 3 | 28.540 | 2 |
| 14.060 | 6 | 28.820 | 2 |
| 14.780 | 58 | 29.340 | 1 |
| 15.360 | 3 | 29.880 | 2 |
| 15.660 | 2 | 30.220 | 1 |
| 16.240 | 1 | 30.580 | 3 |
| 17.100 | 2 | 32.820 | 3 |
| 18.260 | 18 | 33.040 | 2 |
| 18.540 | 10 | 34.640 | 1 |
| 18.900 | 5 | 37.580 | 3 |
| 19.180 | 2 | 39.540 | 3 |
| 19.560 | 4 | 40.500 | 2 |
| 19.700 | 4 | 40.700 | 1 |
| 20.040 | 2 | 42.040 | 2 |
| 20.300 | 2 | 42.480 | 2 |
| 20.860 | 9 | 43.120 | 1 |
| 21.940 | 4 | 43.580 | 1 |
| 22.180 | 4 | 44.520 | 1 |
| 22.540 | 2 | 44.640 | 1 |
| 23.240 | 14 | 44.760 | 1 |
| 23.960 | 2 | 45.320 | 1 |
| 24.240 | 2 | 45.900 | 1 |

5. A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in claim 1 having a transforming point of 149℃.

6. A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in claim 1, which is characterized by an infrared absorption spectrum in potassium bromide with following peaks ($cm^{-1}$):

3314, 3104, 2932, 2858, 2654, 2352, 1609, 1573, 1557,1480,1452, 1407, 1385, 1339, 1309, 1292, 1277, 1260, 1225, 1171, 1150, 1086, 1077, 1029, 996, 970, 911, 898, 870, 828, 816, 773, 701, 679, 630, 615, 586, 550, 526, 457, 435, 411.

7. A polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in claim 1, which is characterized by X-ray powder diffraction pattern (X-ray: Cu K-alpha 1/50kV/300mA; scintillation counter) with following diffraction angle and relative intensity;

| Diffraction angle (2θ;°) | Relative intensity | Diffraction angle (2θ;°) | Relative intensity |
|---|---|---|---|
| 8.580 | 21 | 27.240 | 6 |
| 9.640 | 3 | 28.960 | 3 |
| 10.200 | 100 | 29.580 | 3 |
| 11.960 | 4 | 29.720 | 5 |
| 12.180 | 3 | 30.200 | 4 |
| 15.320 | 14 | 30.440 | 7 |
| 15.980 | 10 | 30.780 | 3 |
| 17.060 | 44 | 31.200 | 10 |
| 17.220 | 15 | 32.240 | 3 |
| 18.080 | 35 | 32.640 | 7 |
| 19.500 | 15 | 34.820 | 7 |
| 21.020 | 14 | 35.140 | 3 |
| 21.920 | 3 | 36.520 | 5 |
| 22.080 | 3 | 38.840 | 5 |
| 22.400 | 10 | 39.900 | 5 |
| 22.700 | 7 | 40.740 | 6 |
| 22.960 | 7 | 41.000 | 12 |
| 23.700 | 5 | 43.740 | 5 |
| 23.880 | 9 | 43.900 | 7 |
| 24.340 | 13 | 46.740 | 3 |
| 24.660 | 10 | 46.820 | 3 |
| 25.480 | 5 | 50.060 | 4 |
| 25.940 | 82 | | |

8. A method for preparing the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in any of claims 2 to 4, which comprises the step of crystallizing 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole in a mixture of methanol and water at a temperature of 60℃ or higher.

9. A method for preparing the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole

as claimed in any of claims 2 to 4, which comprises the step of crystallizing 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole in a mixture of isopropyl alcohol and water at a temperature of 60℃ or higher.

10. A method for preparing the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in any of claims 5 to 7, which comprises the step of crystallizing 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole from a mixture of acetone and water.

11. A method for preparing the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in any of claims 5 to 7, which comprises the step of crystallizing 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole from ethanol.

12. A pharmaceutical composition comprising as an active ingredient the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in claim 1.

13. A pharmaceutical composition comprising as an active ingredient the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in any of claims 2 to 4.

14. A pharmaceutical composition comprising as an active ingredient the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in any of claims 5 to 7.

15. A prophylactic and/or therapeutic agent for the treatment of a disease caused by cyclooxygenase-2 comprising as an active ingredient the polymorph of 5-(4-

aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in claim 1.

16. A prophylactic and/or therapeutic agent for the treatment of a disease caused by cyclooxygenase-2 comprising as an active ingredient the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in any of claims 2 to 4.

17. A prophylactic and/or therapeutic agent for the treatment of a disease caused by cyclooxygenase-2 comprising as an active ingredient the polymorph of 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole as claimed in any of claims 5 to 7.

18. A prophylactic and/or therapeutic agent as claimed in any of claims 15 to 17 wherein the disease caused by cyclooxygenase-2 is at least one member selected from the group consisting of arthritis, gout or ankylosing spondylitis, asthma, bronchitis, menstrual cramp, dysmenorrhea, premature labor, myositis, bursitis, synovitis, skin-related disease, post-operative inflammation, gastrointestinal disease, familial adenomatous polyposis, cancer or metastases of the cancer, cellular neoplastic transformations or metastatic tumor growth, tumor angiogenesis, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, type II diabetes, nephrotic syndrome, Behcet's disease, polymyositis, gingivitis, nephritis, hypersensitivity, ophthalmic disease, disease mediated by influenza or other viral infections, common cold, central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, post-operative

pain, dental pain, muscular pain, neuralgia, lumbago, neck pain, headache, sprains and strains, pain resulting from cancer, glaucoma, osteoporosis, autoimmune disease or diabetic retinopathy.

19. A prophylactic and/or therapeutic agent as claimed in claim 18, wherein the disease caused by cyclooxygenase-2 is arthritis.

20. A prophylactic and/or therapeutic agent as claimed in claim 19, wherein arthritis is rheumatoid arthritis.

21. A prophylactic and/or therapeutic agent as claimed in claim 19, wherein arthritis is osteoarthritis.

22. A prophylactic and/or therapeutic agent as claimed in claim 18, wherein the disease caused by cyclooxygenase-2 is familial adenomatous polyposis.

23. A prophylactic and/or therapeutic agent as claimed in claim 18, wherein the disease caused by cyclooxygenase-2 is cancer or metastases of the cancer.

24. A prophylactic and/or therapeutic agent as claimed in claim 18, wherein the disease caused by cyclooxygenase-2 is central nervous system disorder.

25. A prophylactic and/or therapeutic agent as claimed in claim 24, wherein the central nervous system disorder is Alzheimer's disease.

26. A prophylactic and/or therapeutic agent as claimed in claim 18, wherein the disease caused by cyclooxygenase-2 is osteoporosis.

27. 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole which has the melting point as claimed in claim 2, and the infrared absorption maxima in potassium bromide as

claimed in claim 3, and the X-ray powder diffraction pattern as claimed in claim 4, and the transforming point of 149℃.

28. 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole, which has the infrared absorption maxima in potassium bromide as claimed in claim 6, and the X-ray powder diffraction pattern as claimed in claim 7, and the transforming point of 149℃.

DRAWINGS

FIG. 1

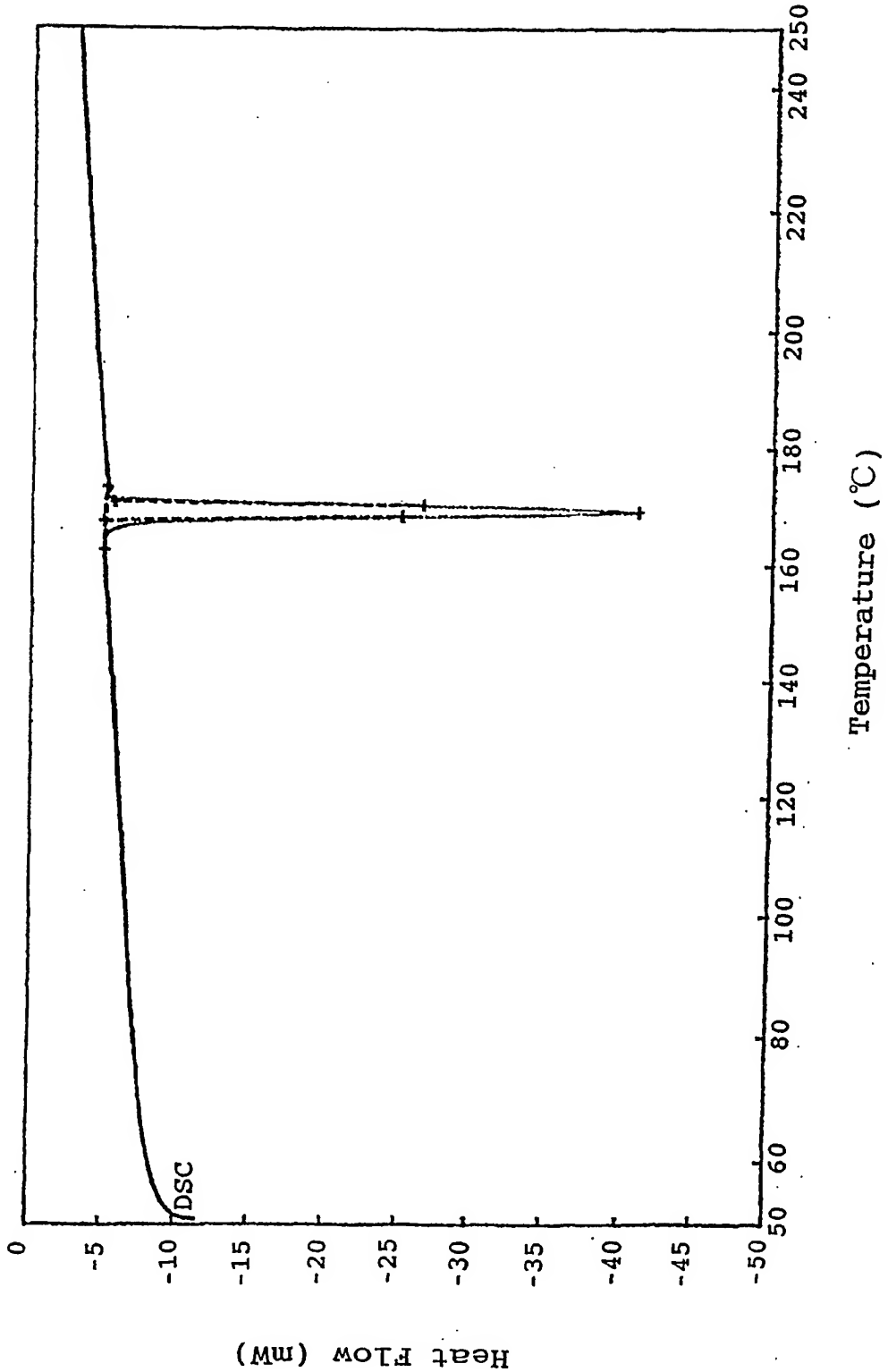


FIG. 2

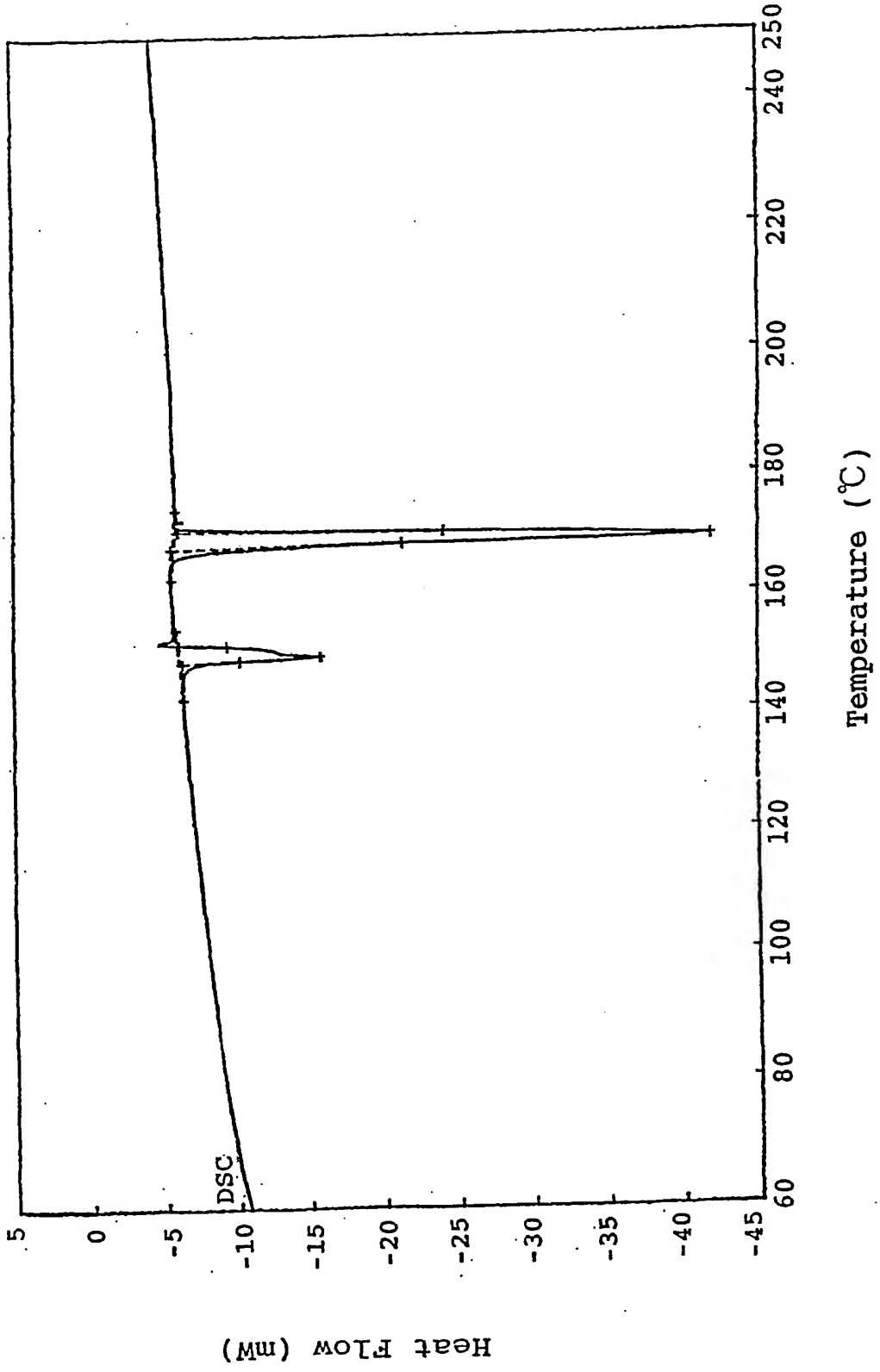

DSC
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
Heat Flow (mW)
60
80
100
120
140
160
180
200
220
240
250
Temperature (℃)

FIG. 3

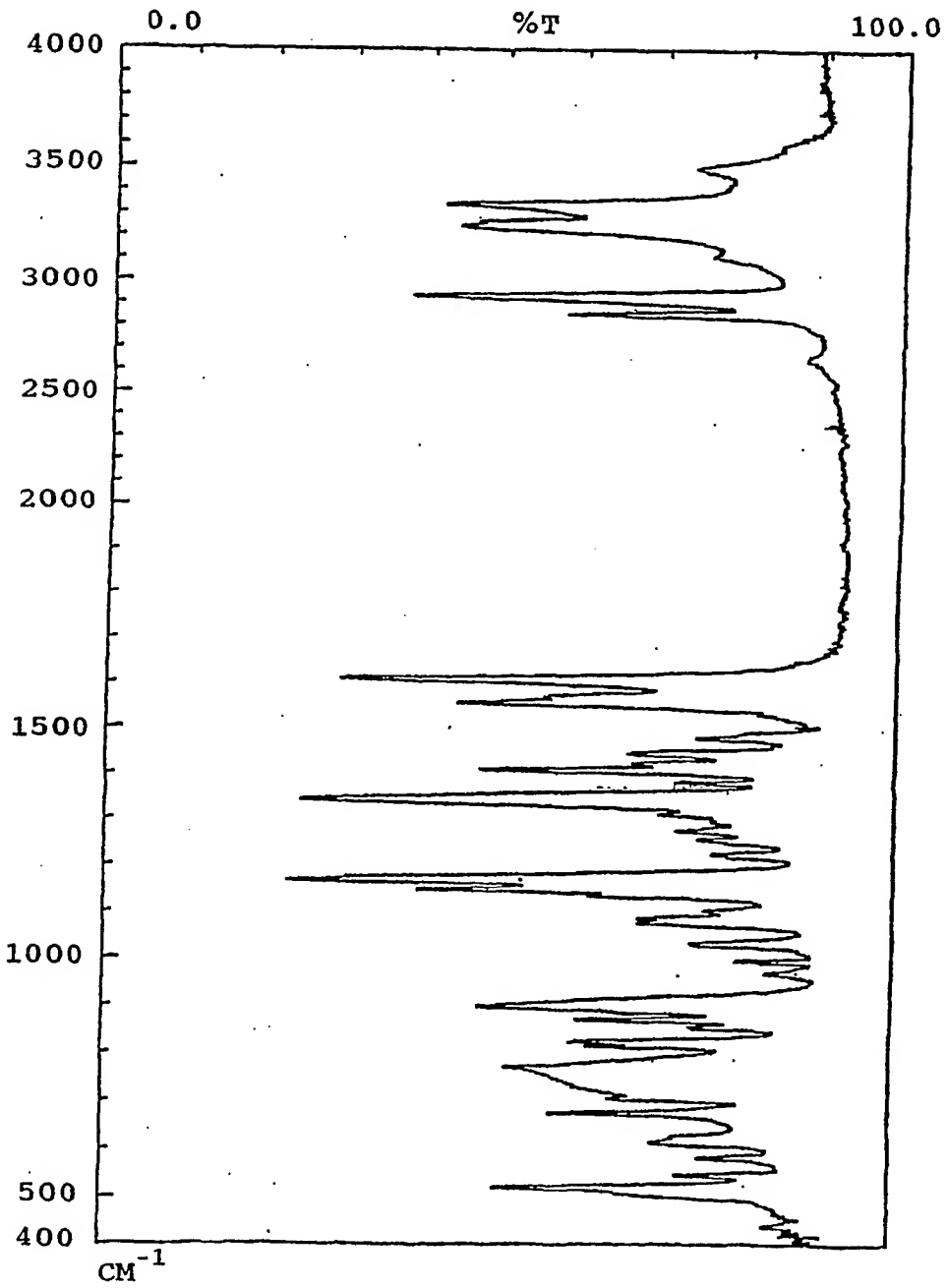


FIG. 4

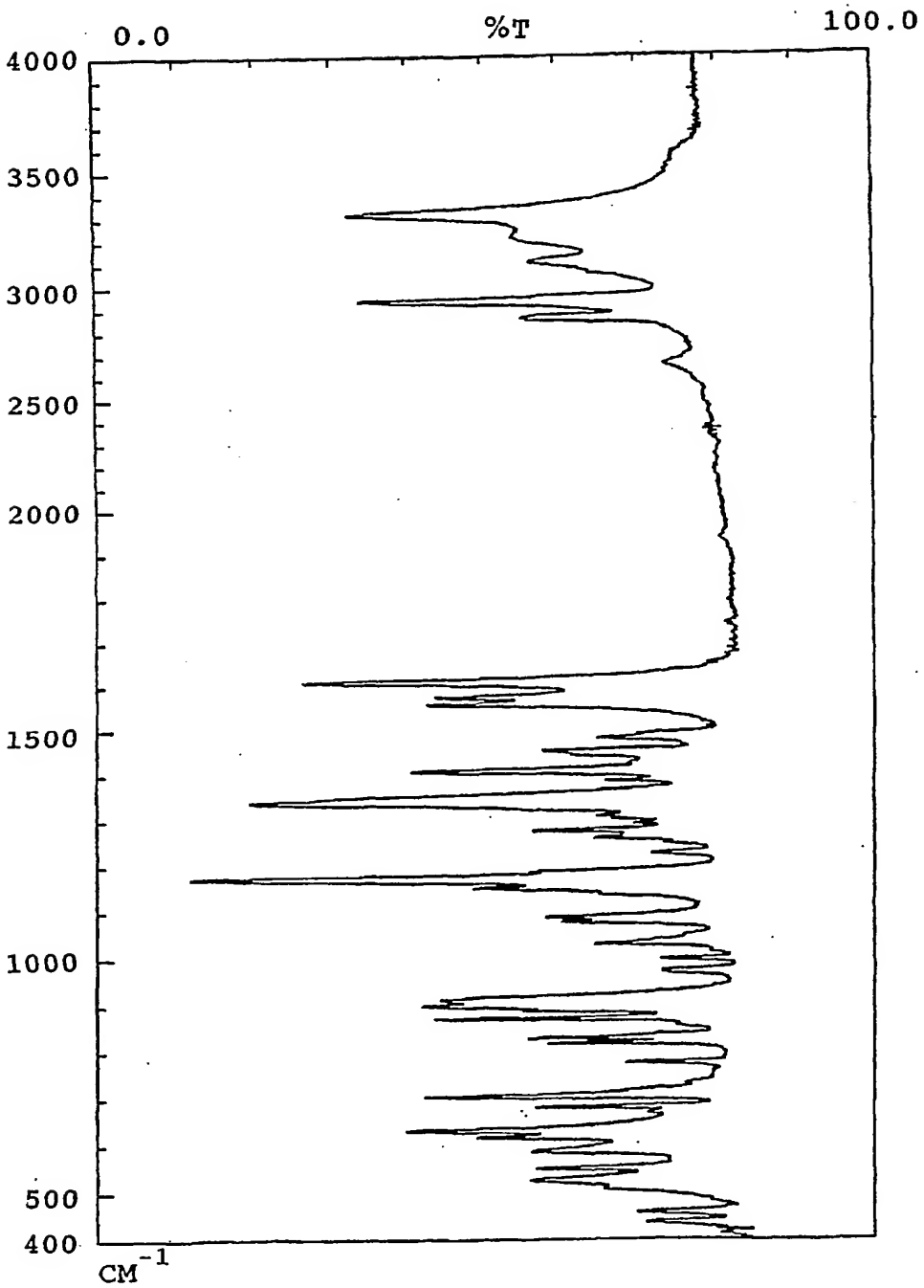
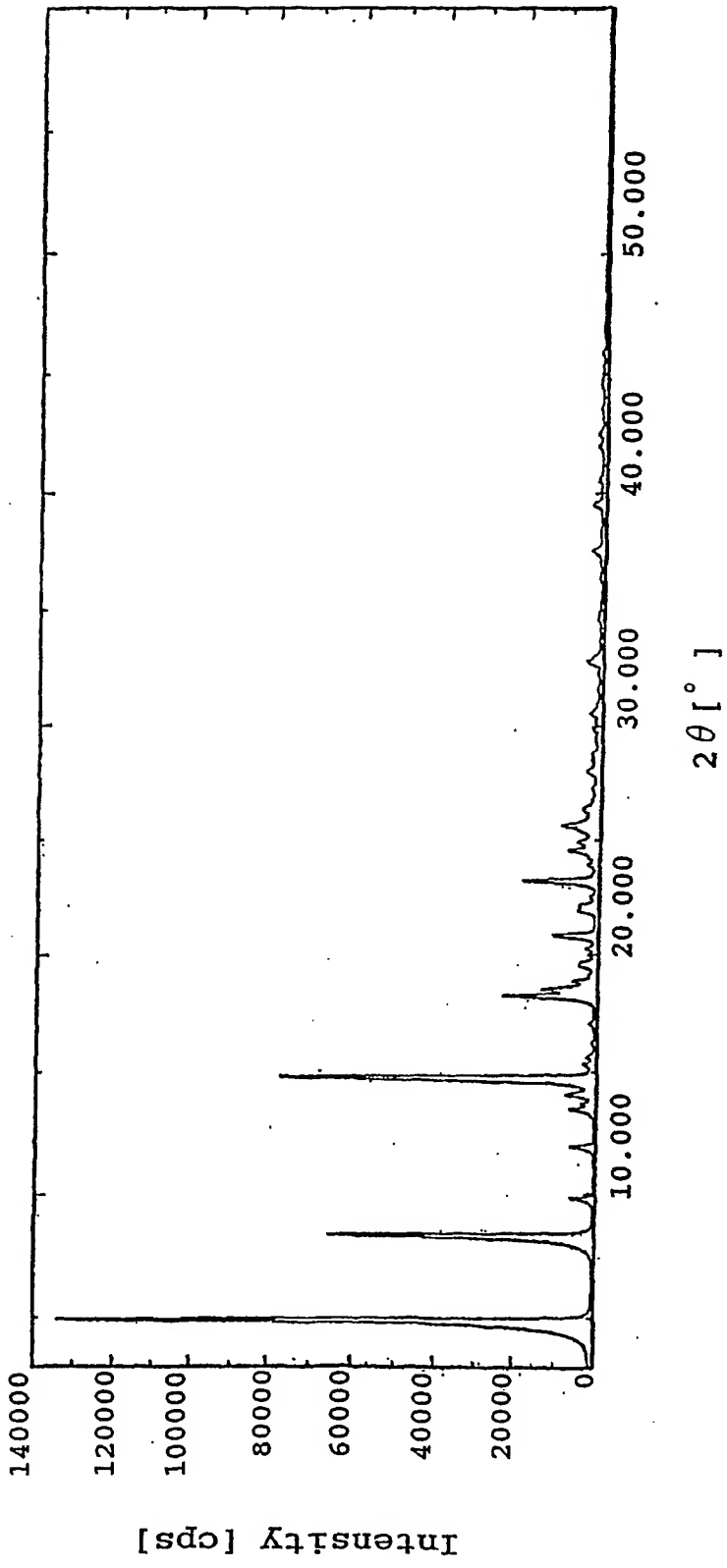


FIG. 5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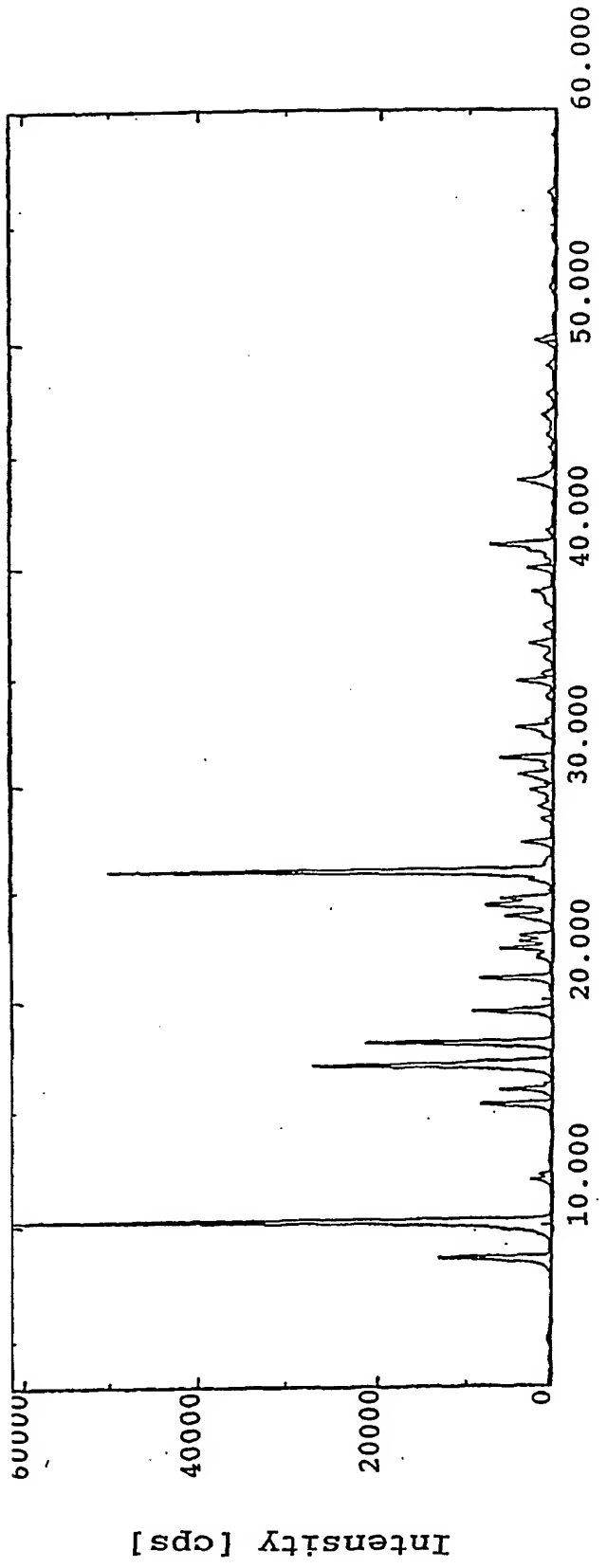
120000
100000
80000
60000
40000
20000
0
10.000
20.000
30.000
40.000
50.000
2θ[°]

FIG. 6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0
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20.000
30.000
40.000
50.000
60.000
2θ[°]

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04343

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl[7] C07D263/32,A61K31/421,A61P43/00,A61P19/02,A61P19/10,A61P11/00,A61P15/00,A61P21/00,A61P17/00,A61P29/00,A61P1/00,A61P35/00(see extra sheet)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl[7] C07D263/32,A61K31/421,A61P43/00,A61P19/02,A61P19/10,A61P11/00,A61P15/00,A61P21/00,A61P17/00,A61P29/00,A61P1/00,A61P35/00(see extra sheet)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS(STN),CAOLD(STN),REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO,96/19463,A1(Japan Tobacco Inc.) 27 June, 1996(27.06.96) & JP,9-52882,A & EP,745596,A1 & US,5994381,A | 1-28 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 13.06.01 | 26.06.01 |

| Name and mailing address of the ISA/JP | Authorized officer |
|---|---|
| Japan Patent Office<br>3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan | TAMOTSU TOMINAGA (Seal) 4P 9840<br>Telephone No. +81-3-3581-1101 Ext. 3490 |

Form PCT/ISA/210 (second sheet) (July 1998)

International application No.
PCT/JP01/04343

(continuation of Box A. )
A61P35/04,A61P25/06,A61P9/00,A61P7/06,A61P29/00,A61P3/10,A61P13/12
(continuation of Box B.)
A61P35/04,A61P25/06,A61P9/00,A61P7/06,A61P29/00,A61P3/10,A61P13/12